Remarks

Claims 8 and 9 are amended to correct informal claim language. Claim 36 is amended to clarify the claimed subject matter. Support for amended claims 13 and 17 is found at page 3, lines 9-10. Support for new claims 47-50 is found at independent claims 7 and 40 and at page 5, lines 21-36. No new matter has been introduced. Claims 7-18, 20, 22, 27-50 are pending.

Rejection under 35 USC §103

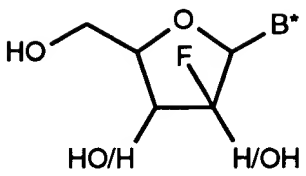
The Office rejected claims 7-18, 20, 22, 27-38 and 40-46 as allegedly prima facie obvious over Martin et al (J. Med. Chem. 33:2137 1990, hereafter Martin) or Robins et al (J. Org. Chem. 39:1564 1974, hereafter Robins) or Ranganathan et al (Tet. Lett. 15:1291 1977, hereafter Ranganathan) or Watanabe et al (J. Med. Chem. 22:21 1979, hereafter Watanabe) or Webb et al (Nucl. Acids Res. 14:7661 1986, hereafter Webb) or Tisdale et al (European Patent Application 0 417 999, hereafter Tisdale) in view of Padyukova et al (Tet. Lett. 28:3623 1987, hereafter Padyukova) and Barton et al (Tet. Lett. 30:4969 1989, hereafter Barton). All references are of record. The Office alleged that the primary references disclosed "unphosphorylated nucleosides" corresponding to the claimed nucleotide analogs and that the secondary references disclosed 5'-methylene phosphonate derivatives of certain nucleosides. The Office asserted that Padyukova taught motivation to make monomers for incorporation into oligonucleotides and that Barton taught motivation to "prepare another derivative that should have comparable or better properties than the free nucleoside analog itself".

Applicants pointed out in amendment B, filed December 15, 1993, that in establishing prima facie obviousness, the Office must show some objective teaching in the cited references that would lead an individual to combine the relevant teachings as evidence of obviousness. In re Lalu 223 U.S.P.Q. 1257 (Fed. Cir. 1987). Both the suggestion and the expectation of success must be founded in the cited art, not in the applicant's disclosure. In re Dow Chemical Co. 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988). Hindsight reconstruction using applicant's disclosure and claims cannot be used as a guide to pick and choose among isolated elements to arrive at the claimed invention. In re Fine 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988). In determining the scope and content of the cited art, the references must be considered in their entirety, as a whole,

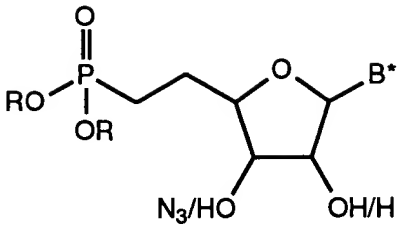
including portions that lead away from the claimed invention. In re Panduit 1 U.S.P.Q. 2d 1593 (Fed. Cir. 1987). A reference cited in support of a rejection under section 103 is not properly relied upon if the reference is from a field of endeavor that is different from the inventor's field and if the reference is not reasonably pertinent to the particular problem with which the inventor is involved. In re Clay 23 U.S.P.Q. 2d 1058 (Fed. Cir. 1992), In re Deminski 230 U.S.P.Q. 313 (Fed. Cir. 1986), 796 F.2d 436, 442. The purposes of both the invention and the cited reference are important in determining whether the reference is reasonably pertinent to the problem the invention attempts to solve. In making a determination that a reference is properly cited, the similarities and differences in structure and function between the reference and the claimed invention must be considered. In re Clay, supra; In re Ellis 177 U.S.P.Q. 526, 527 (C.C.P.A. 1973).

The present rejection is similar to the rejection issued by the Office in the Office action dated August 9, 1993, except that the present rejection now uses Barton in place of the secondary reference by Montgomery et al (J. Med. Chem. 22:109 1979, of record, hereafter Montgomery). Montgomery taught that replacing the 5' phosphate group of 2'-deoxy-5-fluorouridylic acid with a 5' phosphonate group did not yield a molecule with the same biological properties of the parent molecule. Applicants appreciate the omission of Montgomery from the present rejection. Applicants argued in amendment B that this reference taught away from applicant's claimed compounds. The Office has accepted this argument by removing Montgomery from the rejection. Because Montgomery taught away from the presently claimed compounds, The Office is obliged to consider this teaching in evaluating the patentability of the claimed compositions and cannot ignore it by removing Montgomery from the rejection. In re Panduit, supra. Applicants respectfully request reconsideration and withdrawal of the rejection in view of the teaching of Montgomery.

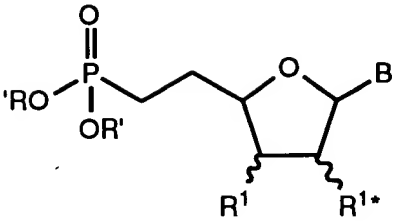
In defining the rejection asserted by the Office, the references are analyzed according to the structures relevant to the analysis. The closest primary and secondary reference structures are shown with corresponding claimed compounds.



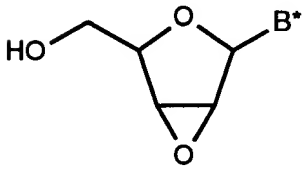
Martin/Ranganathan
Robins/Webb/Tisdale
Watanabe
B* = U, C, 5-FC, A,
DAP, Hx, azC, 5-FU



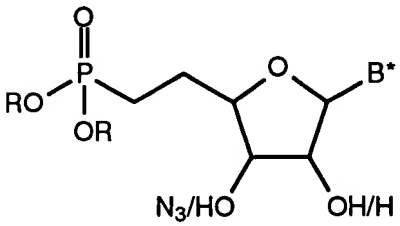
Padyukova/
Barton
B* = A, A^{bz}, U, T



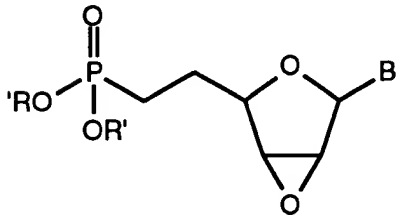
claim 7
R^1 = H, OH
R^{1*} = F, OCH_3



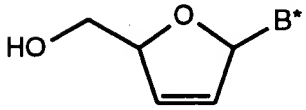
Robins
B* = A, A^{piv}, A^{bz}



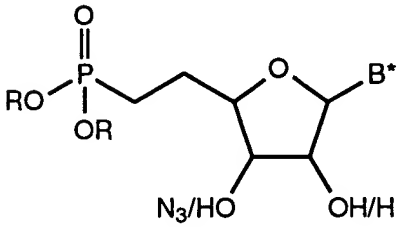
Padyukova/
Barton
B* = A, A^{bz}, U, T



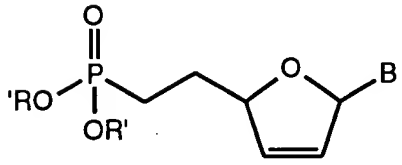
claim 8



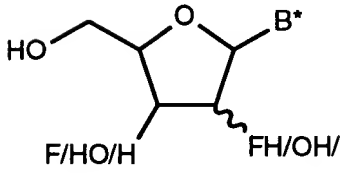
Martin
B* = C, 5MeC



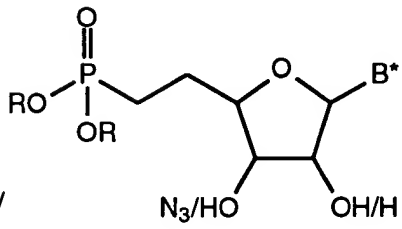
Padyukova/
Barton
B* = A, A^{bz}, U, T



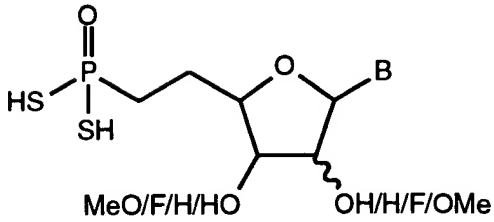
claim 9



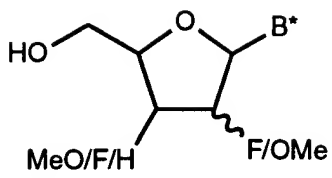
Ranganathan/Watanabe
Webb/Tisdale/Martin/
Robins
B* = A, G, DAP, Hx,
U, C, azC



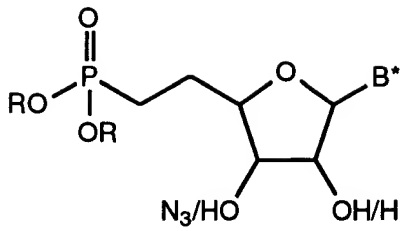
Padyukova/
Barton
B* = A, A^{bz}, U, T



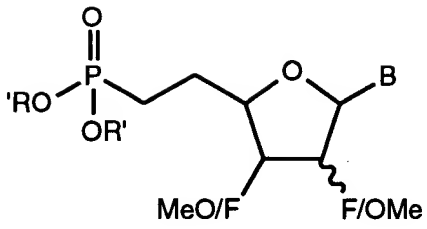
claim 38



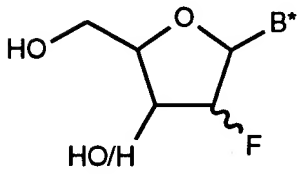
Ranganathan/Watanabe
Webb/Tisdale/Martin/
Robins
B* = A, G, DAP, Hx,
U, C, azC



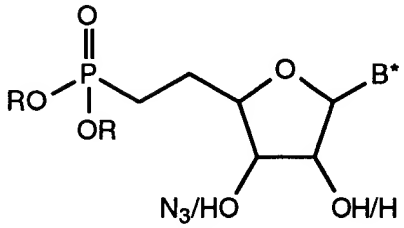
Padyukova/
Barton
B* = A, A^{bz}, U, T



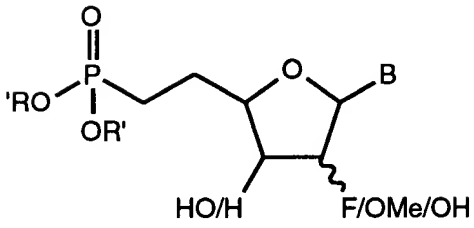
claim 40



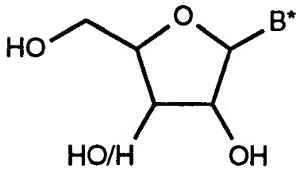
Ranganathan/Watanabe
Webb/Tisdale/Martin/
Robins
B* = A, G, DAP, Hx,
U, C, azC, 5IU, T



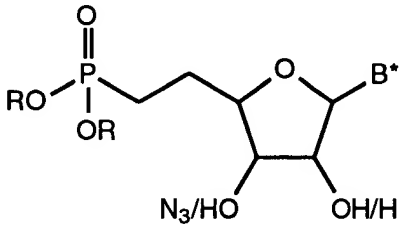
Padyukova/
Barton
B* = A, A^{bz}, U, T



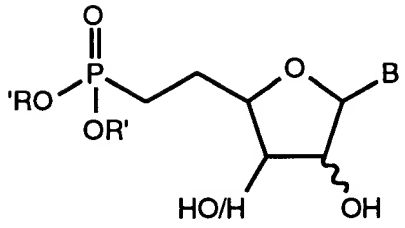
claim 41
B = 5IU, T, G,
MAP



Ranganathan/Watanabe
Webb/Tisdale/Martin/
Robins
B* = A, G, DAP, Hx,
U, C, AzC, A^{piv},C^{Ac}



Padyukova/
Barton
B* = A, A^{bz}, U, T



claim 42
B = G^{ib}, C^{bz}, T^{bz}

Comparing the primary reference structures with the compounds of claims 7-9, 38 and 40-42 (other rejected claims are dependent on these claims) shows that the primary reference compounds are not simply "unphosphorylated nucleosides" that correspond to the claimed compounds. The phosphorylated derivatives of the primary reference compounds are phosphate nucleotide analogs which differ significantly from the claimed phosphonates.

The Barton reference described a single 3' azido nucleotide analog having a 5' phosphonate group and 3'-protected intermediates that were used for its synthesis. However, applicants are claiming no azido compounds and, in order to arrive at any of applicants claimed compounds, the azido or protecting group must be removed from the molecule and replaced with hydrogen, hydroxyl, fluorine or methyl ether. Thus, applicants claimed compounds differ from the Barton compound by lacking the 3' azido or 3' protecting groups. Such structural differences makes applicant's claimed compounds unobvious and patentable over the cited references.

None of the primary references suggest using any phosphonate analog for any purpose. Martin was primarily concerned with the effect of fluorine atoms at the 2' and/or 3' positions of pyrimidine dideoxyribonucleosides which were characterized as inhibitors of HIV reverse transcriptase. Robins described adenosine 2',3'-ribo-epoxides as intermediates useful for synthesis of certain adenosine nucleoside analogs. No other use for the epoxides or for the adenosine analogs were suggested and this reference is thus not properly combinable with any other cited reference. In re Clay, supra. Ranganathan described an improved synthetic route for certain 2'-substituted-2'-deoxyadenosine analogs which were described as potential antiviral or antitumor agents. Watanabe described 2' fluoro substituted pyrimidine nucleosides that were useful for treating certain virus infections. Webb was concerned with incorporating nucleotide analogs having an alkylating pyrimidine base into oligonucleotides. Tisdale described 2'-fluoro substituted purine nucleosides that were characterized as compounds useful for treating certain protozoa and certain viruses associated with respiratory tract infections.

Claim 7. Applicants respectfully traverse the rejection as applied to claim 7 and dependent claims 10-18, 27-29 and 32-34. Padyukova is not properly combined with Martin or Ranganathan or Barton because Padyukova did not deal with therapeutic applications while the remaining references are directed to therapeutics. In re Clay, supra. As previously noted, Montgomery taught that a phosphonate was not biologically equivalent to a phosphate in nucleotide analogs and Robins suggested no use for the

disclosed compounds. Barton and Ranganathan provided no data on biological activity for their described compounds. Barton made no suggestion to use a fluorine or hydroxy substituent at the 2' position. Thus, contrary to the Office's assertion that Barton suggests making other derivatives, the claimed structures were not suggested by the cited references as required. Applicants respectfully submit that the requirement for finding motivation in a reference to make other compounds must amount to more than a bare assertion of biological activity associated with a single untested compound. Both the suggestion and the expectation of success must be found in the cited references (In re Dow Chemical Co., supra) and not in applicant's application (In re Fine, supra).

Applicants submit that Barton could not have provided a motivation to make some of applicant's claimed compounds due to Barton's failure to teach or suggest a synthetic route to the claimed compounds. Barton's synthesis routes could not be used to obtain some of applicant's claimed compounds. Barton does not teach any method to obtain compounds having a fluorine atom at the 2' position, a methyl ether group at the 2' position or a hydrogen at the 3' position. The presence of a fluorine atom at the 2' position would destabilize the free radical to an extent that the addition reaction leading to Barton's compound 8, would not proceed to an appreciable extent. The fluorine at the 2' position also would alter the conformation of the sugar with unpredictable consequences on the stereochemistry of the addition product at the 4' position of 8. Such syntheses were unknown at the time applicants application was filed and applicants were not aware of any route one of ordinary skill in the art would have used to obtain such compounds. In particular, compounds claimed in claims 10-18, which are 2' fluoro species, could not have been synthesized using the teaching of either Barton or, Padyukova, assuming arguendo Padyukova was properly combined.

Applicants respectfully traverse the Office's view that Padyukova provided a motivation to make oligonucleotides. Padyukova described the phosphonates as inhibitors of enzymes whose substrates are esters of phosphoric compounds and alleged at page 3625, paragraph 3 that compounds "11 and 12 can be used for the synthesis of oligonucleotides". Padyukova contained no suggestion to use the compounds for any purpose

other than for enzyme studies or for oligonucleotide synthesis. Thus, as applicants argued in amendment B, Padyukova is nonanalogous art relative to the primary references and relative to Barton. The Office can not properly rely on this reference in rejecting claim 7. In re Clay, supra.

In addition, neither 11 or 12 were suitable for synthesis of oligonucleotides containing more than one 5' methylene linkage because (1) the 2' and the 3' protecting groups were not differentially removable from the molecule, and (2) deprotection of the 2' and 3' positions of 12 would result in deprotection of the purine base at the same time the 2' and 3' positions were deprotected. These considerations would have left one unable to control the point at which such monomers would couple with an oligonucleotide during synthesis. The Padyukova monomers would couple at each of two or three positions, namely the 2' position, the 3' position or at exocyclic amines of purines or pyrimidines having an exocyclic amine. The only oligonucleotides that one could have synthesized would have comprised a single Padyukova monomer at the 3' end of an oligomer. Additional manipulations would have been necessary to prepare properly protected monomers for oligomer synthesis. Padyukova suggested no such manipulation. Because Padyukova's suggestion to make oligonucleotides containing 5' methylene phosphonate linkages was flawed, no motivation to make applicants claimed compounds would have been present.

Finally, Padyukova did not disclose any method that would serve to synthesize applicant's claimed compounds having a fluorine at the 2' position. Applicants are not aware of any synthetic method known at the time the application was filed that one could have used to synthesize 2' fluoro compounds using Padyukova's method. Converting compound 8, at page 3624, to compounds 9 - 14 used a 2' acetate group. A method to convert any of 8 - 14 to a 2' fluoro derivative was not described at the time the application was filed.

Claim 8. The rejection is improper with regard to claim 8 and dependent claim 30 because neither Robins or Padyukova is properly combined with Barton or with each other. In re Clay, supra. The claimed compounds structurally differ from Barton's azido and protected

intermediates to an extent that they are patentably unobvious. In addition, Barton did not suggest any of the claimed compounds as required. Montgomery taught, with biological evidence, that the phosphonate was not equivalent to the phosphate group at the 5' position of nucleotide analogs, which undermined Barton's unsupported assertion.

Claim 9. The rejection is improper with regard to claim 9 and dependent claim 31 because Martin and Pdayukova are not properly combined with each other. In re Clay, supra. The claimed compounds structurally differ from Barton's azido and protected intermediates to an extent that they are patentably unobvious. In addition, Barton did not suggest any of the claimed compounds as required. Montgomery taught that the phosphonate was not equivalent to the phosphate group at the 5' position of nucleotide analogs as discussed above.

Claim 38. None of the cited references, either alone or combined, teach or suggest the structures claimed in claim 38 and dependent claims 43 and 49. The claimed compounds comprise thioate or amidate compounds and no such compound is found in the cited references. The Office has not established a prima facie case of obviousness for the claimed compounds. The rejection of claims 13, 43 and 49 is improper and should be withdrawn. Assuming arguendo the references did disclose the claimed structures, the cited references would not render the claimed compounds obvious because the claimed compounds structurally differ from Barton's azido and protected intermediates to an extent that they are patentably unobvious and Barton did not suggest any of the claimed compounds as required. Montgomery taught that the phosphonate was not equivalent to the phosphate group at the 5' position of nucleotide analogs as discussed above.

Claim 40. Applicants respectfully traverse the rejection as improper with regard to claim 40 and dependent claims 45-46 and 48 because (1) Robins is not properly combined with any other cited reference, (2) Pdayukova and the remaining primary references are not properly combined with each other and (3) Barton and Padyukova are not properly combined. In re Clay, supra. The claimed compounds structurally differ from Barton's azido and protected intermediates to an extent that they are patentably unobvious. In addition,

Barton and the primary references did not suggest any of the claimed compounds as required. Montgomery taught that the phosphonate was not equivalent to the phosphate group at the 5' position of nucleotide analogs as discussed above.

Claim 41. Applicants respectfully traverse the rejection as improper with regard to claim 41 because (1) Robins is not properly combined with any other cited reference, (2) Pdayukova and the remaining primary references are not properly combined with each other and (3) Barton and Padyukova are not properly combined. In re Clay, supra. The claimed compounds structurally differ from Barton's azido and protected intermediates to an extent that they are patentably unobvious. In addition, Barton and the primary references did not suggest any of the claimed compounds as required. Montgomery taught that the phosphonate was not equivalent to the phosphate group at the 5' position of nucleotide analogs as discussed above.

Claim 42. Applicants respectfully traverse the rejection as improper with regard to claim 41 because the Office has not established a prima facie case of obviousness. The claimed nucleotides comprise bases such as N^4-benzoylcytosine, that are not disclosed by any of the cited references. Assuming arguendo, the structures were disclosed, the claims were not obvious because, as applicants have argued above, (1) Robins is not properly combined with any other cited reference, (2) Pdayukova and the remaining primary references are not properly combined with each other and (3) Barton and Padyukova are not properly combined. The claimed compounds structurally differ from Barton's azido and protected intermediates to an extent that they are patentably unobvious. In addition, Barton and the primary references did not suggest any of the claimed compounds as required and Montgomery taught that the phosphonate was not equivalent to the phosphate group at the 5' position of nucleotide analogs.

In view of the foregoing discussion, reconsideration and withdrawal of the rejection is respectfully requested.

Conclusion

Applicants believe the application is in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent at 415-573-4712 (Fax 415-573-4899).

Respectfully submitted,

Daryl D Muenchau

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Gilead Sciences, Inc.
353 Lakeside Drive
Foster City, CA 94404

Dated: 7-22-94